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We report 10 patients (5 familial, 5 sporadic) with facioscapulohumeral muscular dystrophy (FSHD) with onset of facial and shoulder girdle weakness in early infancy. They showed the same broad range of clinical signs and symptoms as can be seen normally in FSHD. In 7 patients Southern blotting with p13E-11 was performed which showed an abnormal *EcoRI* fragment (13–22 kb) in 6 of them. We conclude that early onset FSHD does not differ from regular FSHD clinically or genetically. However, the precise mechanisms involved in the extensive clinical variability of the disease are still unknown. © 1995 John Wiley & Sons, Inc. Key words: facioscapulohumeral muscular dystrophy • infancy-childhood • hearing loss • retinal vasculopathy • DNA rearrangement

MUSCLE & NERVE Suppl 2:S67–S72 1995

## EARLY ONSET FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

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**F**acioscapulohumeral muscular dystrophy is an autosomal-dominant disorder characterized by weakness and atrophy of facial and shoulder girdle muscles. The clinical course is slowly progressive in most cases with successive involvement of abdominal, foot extensor, upper arm, and pelvic girdle muscles.<sup>24</sup> Sporadic cases do occur, but can only be accepted as such if both parents have been examined.<sup>25</sup>

High-frequency hearing loss has been recognized to be part of the disease and to be present in more than 50% of the patients.<sup>5,26</sup> The severity of the hearing loss varies between subjects at any age, but tends to be progressive with gradual involvement of all frequencies.<sup>5</sup> Retinal vascular abnormalities can be identified by fluorescein angiography in many familial and sporadic cases.<sup>9,26</sup> The initial denomination of Coats' disease for this retinal vasculopathy is incorrect as Coats' disease is defined as an usually unilateral, nonhereditary, ex-

udative vascular retinopathy.<sup>26</sup> There appears to be no relationship between the severity of the muscle weakness, and the severity of the hearing loss or the retinal vasculopathy.<sup>26</sup> The pathogenetic mechanism of both hearing loss and retinal vasculopathy in FSHD is still unknown.

In 1990, the FSHD gene was mapped to chromosome 4q35 by linkage analysis.<sup>34</sup> Recently, probe p13E-11, which was isolated from a homeobox domain-containing cosmid and maps to 4q35, has been shown to detect abnormal small fragments with the restriction enzyme *EcoRI* in patients of autosomal-dominant families as well as in sporadic cases.<sup>35</sup> These small fragments were shown to be caused by deletions of homeobox domain-containing repeat units.<sup>8</sup> However, some families with typical FSHD did not show linkage.<sup>2,12</sup> Also, families as well as sporadic cases have been reported that did not show abnormal fragments with p13E-11 suggesting genetic heterogeneity or mutations resulting in nondetectable rearrangements.<sup>13,31,33,35</sup>

In most FSHD patients the first symptoms of muscle weakness are noticed at the end of the first or in the second decade.<sup>24,30</sup> A severe form of FSHD in young children has been frequently reported.<sup>1,7,10,11,14–19,21–23,27–29,32,36,37</sup> Brooke was the first to describe infantile FSHD as a special form of the disease and he even suggested a specific clinical course and mode of inheritance in this presentation of FSHD.<sup>3</sup> Indeed, many of these infantile cases are sporadic, or in the hereditary cases only slight facial weakness can be observed in

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Presented in part at the International Symposium on Facioscapulohumeral Muscular Dystrophy, Kyoto, Japan, July 10, 1994.

Acknowledgments: The genetic studies were supported by the Prinses Beatrix Fonds, The Hague, The Netherlands. The clinical studies were supported by the Association Française contre les Myopathies, Paris, France.

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CCC 0148-639X/95/S20S67-06  
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one of the parents. Initially, his ideas of clinical and genetic heterogeneity were also supported by the fact that, in many of these infantile cases, high-frequency hearing loss and retinal vascular abnormalities were reported, and mental retardation in some of them.

As part of a large clinical and genetic study of FSHD in The Netherlands, we searched for patients with onset of facial and shoulder girdle weakness in early childhood. Our purpose was to determine the clinical and genetic features of these early onset cases and to be able to answer the question of whether this form of FSHD really is a distinct entity or just part of the FSHD spectrum. In familial cases, at least one affected family member had electromyography and muscle biopsy findings compatible with FSHD. Sporadic cases were accepted as such only if both parents and siblings were examined physically; if this has not been done, it is explicitly stated in the text.

## CASE REPORTS

We identified 10 patients with early onset FSHD. Six cases have been reported earlier.<sup>6</sup> Four additional cases are described below. The clinical and genetic data of all 10 patients are summarized in Tables 1 and 2.

**Case 7.** This mentally retarded 20-year-old male could not close his eyes from early infancy and his mother noticed him to be floppy. At the age of 2 he could walk without support. Audiological examination was performed at age 3 because of delayed speech, but was reported to be normal. He had never been able to whistle or to drink through a straw. At the age of 9 he had corrective surgery for a hanging lower lip. In the same period difficulties with his shoulder function were noticed. He visited

a school for mentally retarded and, upon examination, he had low-set malformed ears, a high-arched palate, divergent strabism with slight proptosis, and facial weakness with an inability to close his eyes fully (Fig. 1). Shoulder girdle weakness was present with severe limitation of abduction and anteflexion of both arms. There was some atrophy of the sternocleidomastoid and pectoralis muscles. Flexion contractures of the proximal interphalangeal joints of the hands were noticed. A thoracic kyphoscoliosis was observed with increased lumbar lordosis, but no scapular winging. He had a waddling gait and weakness of the left foot extensors. Hearing was not obviously impaired: he could hear a whispering voice at a 4-m distance.

The patient is from a family with autosomal-dominant FSHD. His 49-year-old mother and his grandfather are affected; two younger brothers aged 18 and 15 years, respectively, do not have any signs or symptoms of muscle weakness. Southern blot analysis with p13E-11 in this family revealed an abnormal 18-kb fragment in this boy and his affected mother.

**Case 8.** This 17-year-old boy reportedly always slept with his eyes open. Early motor development was normal but, at the age of 3 years, hyperactivity, clumsiness, and a speech delay were noticed. He appeared to be mildly mentally retarded at the age of 5 and went to a special school. Neurological examination at age 7 showed facial and shoulder girdle weakness, scapular winging, increased lumbar lordosis, and a waddling gait. Serum CK level was 683 U/L (normal < 100 U/L); electromyography showed no abnormalities and muscle biopsy findings were compatible with a myopathy. Audiometry revealed right-sided hearing loss of 60 db at

**Table 1.** Clinical data of 10 early onset cases of FSHD.

Case no./sex/age (yr)	Severity of disease*	Serum CK (U/L)	EMG	Muscle biopsy	Mental retardation	Hearing loss	Retina abnormal
1/F/30	Moderate	—	—	—	—	—	—
2/M/5	Moderate	—	—	—	±	—	—
3/M/8	Mild	—	—	—	—	—	—
4/M/30	Severe	1265	Myopathic	Myopathy	—	—	—
5/F/18	Severe	—	—	—	—	+	+
6/M/12	Moderate	426	Myopathic	—	—	+	—
7/M/20	Moderate	—	—	—	+	—	—
8/M/17	Severe	683	Normal	Myopathy	+	+	—
9/M/11	Moderate	587	Normal	Dystrophy	+	+	+ (Coats)
10/M/13	Moderate	—	Myopathic	—	—	—	—

FSHD: facioscapulohumeral muscular dystrophy; CK: creatine kinase, normal value <100 U/L; EMG: electromyography.

\*Classification of severity of disease as "mild," "moderate," or "severe" according to Lunt et al.<sup>20</sup>

Cases 1–6 have been described earlier.<sup>6</sup>



**Table 2.** Genetic data of 10 early onset cases of FSHD

Case no/sex/age (yr)	Familial/ sporadic	Parent affected	Severity of disease* in affected parent	Size of <i>Eco</i> RI fragment (kb)
1/F/30	Familial	Father	Mild	22
2/M/5	Familial	Father	Mild	15
3/M/8	Familial	Father	Moderate	16.5
4/M/30	Familial	Father	Moderate	—
5/F/18	Sporadic	—	—	13
6/M/12	Sporadic	—	—	No small fragment
7/M/20	Familial	Mother	Moderate	18
8/M/17	Sporadic	—	—	13.5
9/M/11	Sporadic	—	—	—
10/M/13	Sporadic	—	—	—

FSHD: facioscapulohumeral muscular dystrophy.

\*See Table 1.

4000 Hz. Since then the disease clearly progressed: at age 12, walking stairs and standing up from a chair had become very difficult. Examination at this time showed a bilateral foot drop in addition to the other described features.

His parents and elder sister were healthy and had no signs or symptoms of muscle weakness. Southern blot analysis with p13E-11 showed a new *Eco*RI fragment of 13.5 kb in the boy, which was not found in any of the other family members.

**Case 9.** This mentally retarded 11-year-old boy had a slow motor development; he walked without support at the age of 2½ years. It was noticed that he always kept his mouth open. At the age of 1 year, retinal exudative teleangiectasis with left retinal detachment led to a diagnosis of bilateral Coats' disease. Cryotherapy was performed on sev-

eral occasions. In the first years recurrent middle ear infections were initially blamed for impaired hearing function. Audiometry at the age of 3 years showed bilateral high-frequency hearing loss of 65 dB, and hearing aids were prescribed. Examination at age 11 showed a retarded boy with an opened mouth and immobile face due to facial weakness and atrophy, scapular winging, shoulder girdle weakness and atrophy, and increased lumbar lordosis with protruding of the abdomen. Gower's sign was positive. His IQ was in the 60–80 range. Serum creatine kinase was 587 U/l (normal < 100 U/L). Electromyography, computer tomography of several muscle groups, and magnetic resonance brain imaging all gave normal results. Muscle biopsy findings were compatible with muscular dystrophy.

Case 9 is the only child. There is no family his-



**FIGURE 1.** Case 7. A 20-year-old mentally retarded male with early onset facioscapulohumeral muscular dystrophy. His mother is also affected.



tory of muscle weakness, but the parents have not been examined physically. DNA analysis is not available at present.

**Case 10.** This 13-year-old boy slept with his eyes open from early infancy and he had never been able to whistle. At the age of 6 he had a blow on his left eye. After this accident facial asymmetry with drooping of the left corner of the mouth and dysarthria were noticed by his parents and speech therapy was started. From the age of 12 years, progressive muscle weakness of the left shoulder was observed causing increasing difficulties with gymnastics at school. His intelligence is above average. On examination he had severe symmetrical facial weakness, and weakness and atrophy of the shoulder girdle and upper arm muscles with scapular winging. The deltoid muscles were relatively spared. He had a flattened lumbar lordosis and a waddling gait, but otherwise no weakness or atrophy of the lower extremities was found. Hearing function seemed to be normal, but audiometry was not performed. Electromyographic findings were compatible with a myopathy.

There was no family history of a neuromuscular disorder. Both parents are healthy and showed no abnormalities at examination. Two other siblings were reported to have no signs or symptoms of muscle weakness, but they were not physically examined. DNA analysis has not yet been performed.

## DISCUSSION

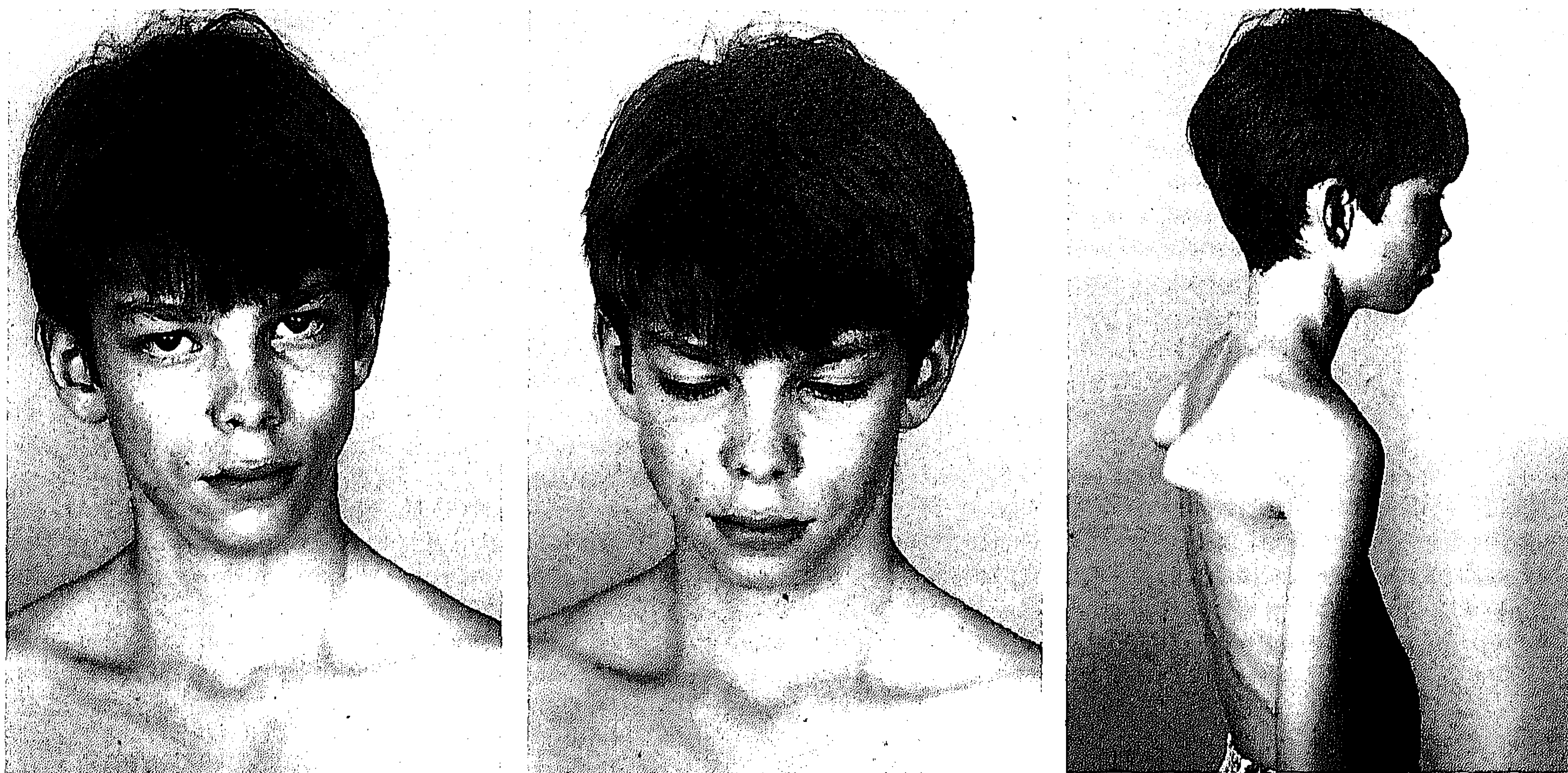
Several clinical observations led researchers to formulate the question of whether FSHD might be a genetically heterogeneous disorder. One of the most peculiar observations is that of infantile or early onset FSHD, which is characterized by progressive muscle weakness leading to severe disability at young age, and is frequently associated with high-frequency hearing loss and retinal vasculopathy ranging from severe Coats' disease to mild tortuosity of retinal vessels. At least 55 early onset cases have been published in the literature.<sup>1,7,10,11,14-19,21-23,27-29,32,36,37</sup> It appears, however, that these cases are not a real representation of FSHD in early childhood and most of them are severely affected cases by both ascertainment and publication bias. Otorhinolaryngologists tend to report on patients with severe hearing loss,<sup>16,22</sup> ophthalmologists on patients with Coats' disease,<sup>14,27</sup> and neurologists on patients with severe muscle weakness.<sup>1,7,15,23</sup> Sporadic early onset cases seem to be more severely affected than familial

ones, but this is probably due to ascertainment bias as less affected sporadic cases often go undiagnosed. This bears relevance to the question of whether this early onset FSHD really is a clinically and/or genetically distinct disorder or just the end of the clinical spectrum of FSHD.

We report 10 patients with onset of facial and shoulder girdle weakness in early childhood. Six of them were identified by a careful search in a large patient material in The Netherlands and have been described earlier.<sup>6</sup> Of these 10 cases, 5 were familial and 5 sporadic. Clinical course and rate of progression were not clearly different between the two groups. High-frequency hearing loss and retinal vasculopathy were only found in sporadic cases: hearing loss in 4, and retinal vasculopathy in 2. However, audiometry has not been performed in all, and retinal fluorescein angiography, which is necessary to identify subtle abnormalities of the retinal vessels, was done in only 3. So, clinically, our early onset cases represent the full spectrum of FSHD, including the presence of hearing loss and retinal vasculopathy in some of them.

Only part of the problem was resolved by the recent finding that hearing loss and retinal vasculopathy are part of FSHD. It is still unknown which mechanisms are responsible for the broad clinical spectrum of FSHD, and one might speculate about genetic mechanisms that might be involved. It has been recently shown that FSHD is associated with DNA rearrangements detected by the probe p13E-11.<sup>35</sup> This probe detects a polymorphic chromosome 4-specific *Eco*RI fragment, which is usually larger than 28 kb in normal individuals, but shorter (14-28 kb) in FSHD patients. These rearrangements are due to deletions of integral copies of a 3.2-kb tandemly repeated unit.<sup>8</sup> Trinucleotide repeats are known to be involved in other dominant disorders such as fragile X syndrome, myotonic dystrophy, and Huntington's disease. Increasing amplification of these trinucleotide repeats in the mutant gene in following generations cause these diseases to become clinically manifest at an earlier age in succeeding generations, a mechanism called anticipation. Deletion, instead of amplification, of the 3.2-kb repeats in FSHD patients may well play a role in its pathogenesis, but it is unlikely that anticipation is present in FSHD because within families with autosomal-dominant FSHD the abnormal DNA fragment always has the same size despite large variability in phenotypic expression. Earlier reports concluded that there is no correlation between the size of the *Eco*RI fragment and disease severity in sporadic cases.<sup>13</sup>





**FIGURE 2.** Case 6. A 12-year-old boy with early onset FSHD with severe facial and shoulder girdle weakness. His parents have no signs of muscle weakness.

A genetic mechanism, which may mimic anticipation if the parents are clinically not affected, is germ-line mosaicism. Identical small *Eco*RI fragments have been found in affected siblings, but not in their healthy parents, which is very suggestive of germ-line mosaicism.<sup>13,33</sup> Recently, a male patient was identified with a nonaffected father showing a weak small fragment of the same size as in his daughter, suggesting somatic mosaicism (Bakker and Wijmenga, personal communication).

We found small *Eco*RI fragments ranging from 13 to 22 kb in 6 of 7 early onset cases (Table 2). Case 6 did not show an abnormal fragment: the patient had all the clinical hallmarks of FSHD (Fig. 2) and high-frequency hearing loss. His parents and two siblings were normal at examination. In our group of early onset cases there was a tendency of fragments to be shorter in more severely affected cases. The question remains why some families and sporadic cases do not show an abnormal fragment. Hypothetically, this might be due to a point mutation or a very large deletion, but genetic heterogeneity cannot be excluded.

Genomic imprinting, the asymmetrical impact of one parental chromosome of an autosomal pair, seems not to play a role in early onset FSHD. From the case reports in the literature, as well as from our own material, one may conclude that there is no relationship between the occurrence and severity of the disease, and the sex of the affected parent. Still, there is the possibility of a modifying gene, even in the unaffected parent, as proposed by Brooke.<sup>4</sup>

We conclude from this study that neither clinically nor genetically early onset FSHD differs from adult onset FSHD. The mechanisms responsible for the broad clinical spectrum of FSHD still have to be identified and definite answers can only be given after the FSHD gene has been found. In the mean time it would be worthwhile to investigate all reported patients with early onset FSHD, especially sporadic cases with mental retardation, hearing loss, and retinal vasculopathy, and their family members with probe p13E-11 for the presence of abnormal *Eco*RI fragments.

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